C1)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,440	10/15/2003	Rosanne M. Crooke	ISPH-0595US.P1	4998

36441 7590 01/26/2005

MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/684,440	CROOKE ET AL.
	Examiner	**Art Unit**
	Amy H Bowman	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-25,30 and 32-35* is/are pending in the application.

4a) Of the above claim(s) *20,21,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-19, 22, 25, 30 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date *10/15/03; 2/23/04*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without prejudice of group II in the reply filed on 1/3/2005 is acknowledged.

Applicant's election with traverse of SEQ ID NO:23 in the reply filed on 1/3/2005 is acknowledged. Applicant traverses the restriction to individual sequences. Each sequence is considered to be separate and distinct, involving a separate search, as explained in the Official Office Action mailed on 12/02/2004.

Please note that the restriction requirement was not a species election. Applicant has elected SEQ ID NO:23. As demonstrated in the specification, table 1, SEQ ID NO:23 is targeted to the coding region. Therefore, in electing SEQ ID NO:23, applicant has also elected the coding region, which corresponds to SEQ ID NO:23. Claims 20, 21, 23 and 24 are drawn to methods comprising an antisense nucleic acid that is specifically hybridizable with a 5'-untranslated region, start region, stop region or 3'-untranslated region, respectively. Claims 20, 21, 23 and 24 are withdrawn as they do not correspond to the region targeted by the elected sequence and therefore do not read on the elected invention. Additionally, SEQ ID NOS: 11, 12, 14, 16, 17, 18, 19, 21, 25, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43 and 45 are withdrawn as being drawn to non-elected inventions.

The requirement for restriction is still deemed proper and is therefore made FINAL.

Claims 1, 26-29 and 31 have been cancelled. Upon the amendments made to claims 2-25, 30 and 32-35 on 1/3/2005, claims 2-19 and 22 will be examined with the elected method claims of group II, claims 25, 30 and 32-35 and SEQ ID NO:23.

In the restriction set forth on 12/2/2004, Claim 1 was indicated as a linking claim. In this amendment, applicant cancelled claim 1 and amended claims 25 and 30 such that claims 25 and 30 are now linking claims with respect to the multiple sequence inventions claimed. Although claim 1 has been cancelled, a similar restriction will now apply to claims 25 and 30, which are now the linking claims. Claims 25 and 30 link each of the target regions with their corresponding sequences. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 25 and 30. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. The linking claims, 25 and 30, have been rejected, so the sequences have not been rejoined.

Applicant timely traversed the restriction (election) requirement in the reply filed on 1/3/2005.

Specification

The disclosure is objected to because it contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because it contains three sequences on page 62 of the specification that are not identified by SEQ ID NOs. Failure to comply with these requirements will result in abandonment of the application under 37 C.F.R. § 1.821(g). The sequences do not appear to be present in the CRF as filed. If the sequences are not in the CRF, it must be updated. Applicant must verify that the entire application is compliant with 37 C.F.R. §§ 1.821-1.825.

Information Disclosure Statement

It is noted that an Information Disclosure Statement was filed on 1/10/2005, but it was not available for examiner review. Once the image is available, it will be considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-19, 22, 25, 30 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims broadly read on any compound targeted to any nucleic acid sequence encoding any version of apolipoprotein(a) from any organism. Although the specification describes antisense sequences (i.e. table 1), there is no specific description provided of a sequence to any other versions or species of apolipoprotein(a) which will bind to any other apolipoprotein(a) sequence, and inhibit the expression of any other apolipoprotein(a). The skilled artisan would not be able to envisage a sufficient number of oligonucleotides targeted to other species of apolipoprotein(a) such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing. The specification as filed does not describe a sufficient number of antisense, DNA and RNA oligonucleotide sequences to describe the structure and sequence of a sufficient number of species encompassed in the instantly claimed genus. The specification only teaches antisense sequences which target apolipoprotein(a) SEQ ID NO:4 and do not meet the scope of the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification, while providing information on some antisense sequences to SEQ ID NO:4, does not provide a description of other species or guidance as to what antisense sequence for which version of apolipoprotein(a) will target and inhibit a sufficient number of species of apolipoprotein(a) to describe the full genus claimed.

Claims 2-19, 22, 25, 30 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Instant claims 2-19 and 22 are drawn to the method of claim 25, which encompasses the *in vivo* inhibition of apolipoprotein(a) expression. Claim 25 is drawn to a method of inhibiting the expression of apolipoprotein(a) in a cell or tissue comprising contacting said cell or tissue with a compound targeted to a nucleic acid encoding apolipoprotein(a). Claims 30 and 32-35 are drawn to a method of treating an animal having a disease or condition associated with apolipoprotein(a) comprising administering a therapeutically or prophylactically effective amount of a compound targeted to a nucleic acid encoding apolipoprotein(a) so that the expression of apolipoprotein(a) is inhibited. Claims 2-19, 22, 25, 30 and 32-35 encompass *in vivo* delivery of the oligomeric compound. Although the specification is enabling for inhibition of apolipoprotein(a) expression *in vitro*, it does not reasonably provide enablement for the inhibition of such cells *in vivo* or the treatment of an animal.

The state of the prior art is such that gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Branch (TIBS 1998, vol. 23, p. 45-50), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNS can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

In addition to the more general hurdles that are recognized by the art in antisense applications, apolipoprotein(a) has additional factors specific to this target recognized in the field as unpredictable. For example, Morishita et al. discuss that it is difficult to use the antisense strategy to decrease apolipoprotein(a) because the structure of the apolipoprotein(a) gene has a very high degree of homology to the plasminogen gene (see page 1899, first column) and, therefore, it is unpredictable to find antisense oligos to specifically inhibit apolipoprotein(a). Morishita et al. further discuss that antisense technology and ribozyme oligonucleotides are not useful to inhibit apolipoprotein(a) because it is difficult to select antisense sequences around ATG sites that are most commonly and effectively used as antisense sequences because the structure of the apolipoprotein(a) gene around ATG sites is completely identified to the plasminogen gene and that antisense sequences against apolipoprotein(a) can inhibit plasminogen gene expression as well (see page 1903, first column).

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples of human bladder carcinoma cells, human lung carcinoma cells, human neonatal dermal fibroblasts, and human embryonic keratinocytes being treated with antisense compounds *in vitro* (specification pp. 68-70), however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of a target gene. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the *in vitro* inhibition of apolipoprotein(a) in cell culture, the specification is not enabling for claims 2-19, 22, 25, 30 and 32-35, which encompass the *in vivo* inhibition of apolipoprotein(a) in any organism as the art of inhibiting gene expression by introducing oligonucleotides into an organism is neither routine nor predictable. Although a number of prophetic examples are given in the specification *in vivo*, these have not been reduced to practice nor has guidance been given to successfully practice the method *in vivo*. For example, as stated in the specification, page 87, although transgenic mice expressing human apolipoprotein(a) exist, they fail to assemble LP(a) particles because of the inability of human apolipoprotein(a) to associate with mouse apolipoprotein B, resulting in the need to engineer mice expressing both human apolipoprotein(a) and human apolipoprotein B transgenes. This demonstrates that there are differences between the mouse and human systems and the *in vivo* delivery in other organisms would not be predictable. In order to practice the claimed invention *in vivo* in all organisms, a number of variables would have to be optimized, including 1). determining what sequences would constitute sequences capable of binding to apolipoprotein(a) and what sequences would actually bind to apolipoprotein(a) and form a strong enough complex that they would be effective at modulating apoptosis, 2). the form of the antisense or decoy oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the antisense or decoy oligonucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of antisense or decoy oligonucleotide that would need to be delivered in order to bind a sufficient amount of apolipoprotein(a) to modulate apoptosis once it reached the proper cell and 5). ensuring the antisense or decoy oligonucleotide remains viable in a cell for a period of time that allows modulation of apoptosis to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense or decoy oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 2-19, 22, 25, 30 and 32-35 are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Claim 19 is directed to non-elected inventions. Specifically, SEQ ID NOS: 11, 12, 14, 16, 17, 18, 19, 21, 25, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43 and 45 are not drawn to the elected invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 5, 7, 10-13, 14, 16, 18, 22 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Morishita et al. Instant claims 2, 4, 5, 7, 10-13, 14, 16, 18 and 22 are drawn to the method of claim 25, which is drawn to a method of inhibiting the expression of apolipoprotein(a) in a cell or tissue comprising contacting said cell or tissue with a compound targeted to a nucleic acid encoding apolipoprotein(a). Instant claims 2, 4, 5, 7, 10-13, 14, 16, 18 and 25 are drawn to the method of claim 25, wherein the compound is 12 to 50 nucleobases in length; wherein the compound comprises an oligonucleotide; wherein the oligonucleotide is an antisense oligonucleotide, DNA oligonucleotide or RNA oligonucleotide; wherein the compound is at least 80%, 90%, 95% or 99% complementary with said nucleic acid molecule encoding apolipoprotein(a); wherein the compound has at least one modified internucleoside linkage; wherein the compound has at least one phosphorothioate internucleoside linkage; wherein said compound preferentially binds to a nucleic acid sequence of apolipoprotein(a) and does not bind, or binds weakly to a nucleic acid sequence encoding plasminogen; or wherein the coding region is targeted, respectively.

Morishita et al. disclose three phosphorothioate modified ribozyme oligonucleotides and one DNA based oligonucleotide, 42 base pairs in length, targeted to kringle 4 of apolipoprotein(a) (see page 1899, methods and figure 1A). Morishita et al. also disclose that the expression of ribozyme oligonucleotides targeting human apolipoprotein(a) inhibited human apolipoprotein(a) protein expression in HepG2 cells (see figures 2A and 2B), but not plasminogen concentrations (see figure 3A). Morishita et al. further disclose that ribozyme inhibition of human apolipoprotein(a) abolished the mitogenic action of conditioned medium in HepG2 cells. The hybridizing arms of the ribozyme comprise a region that is at least 99% complementary with a nucleic acid molecule encoding apolipoprotein(a), which meets the limitations of instant claims 10-13. The ribozymes taught by Morishita et al. are targeted to the coding region (see Figure 1A and results, paragraph 1).

Therefore, the ribozyme oligonucleotides and method of inhibition taught by Morishita et al. meets the limitations of instant claims 2, 4, 5, 7, 10-13, 14, 16, 18, 22 and 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-18, 22 and 25, are rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al, in view of Frank et al., and further in view of Baracchini et al. (U.S. patent 5,801,154).

Morishita et al. teach that phosphorothioate modified ribozymes targeted to the coding region of apolipoprotein(a). The ribozymes taught be Morishita et al. are 42 base pairs in length.

Morishita et al. do not teach the usage of antisense oligonucleotides to target a nucleic acid encoding apolipoprotein(a).

Frank et al. teach the usage of apolipoprotein(a) antisense RNA to inhibit apolipoprotein(a) synthesis (see abstract, figure 1). Antisense transduction caused a significant reduction in apolipoprotein(a) secretion (see results). The full length antisense RNA taught by Frank et al. is silent with regards to specific structure.

Additionally, Baracchini et al. teach antisense oligonucleotides formulated in pharmaceutical compositions (column 4) and the modification of antisense oligonucleotides, such as phosphorothioates, 2'-O-methoxyethyl sugar moieties, and 5-methylcytosine nucleobase modifications (columns 6 and 7). Additionally, Baracchini et al. teach the usage of chimeric oligonucleotides containing two or more chemically distinct regions (column 8). Baracchini et al. teach antisense oligonucleotides that target the coding region and that are 8-30 nucleobases in length.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make an antisense oligonucleotide to apolipoprotein(a) as taught by Frank et al. to inhibit apolipoprotein(a) as shown by Morishita et al. in combination with the modifications and oligonucleotide length taught by Baracchini et al. There would have been a motivation to inhibit apolipoprotein(a) due to its known role in various diseases, such as atherosclerosis, as demonstrated by Morishita et al. Additionally, it would have been obvious to inhibit apolipoprotein(a) by targeting the coding region, as demonstrated by Morishita et al. Due to the size and accessibility of the coding region, there would be a reasonable expectation of success to target an antisense oligonucleotide to this region, as demonstrated by Baracchini et al. Since Morishita et al. have used ribozymes and Frank et al. have used antisense RNA to inhibit the expression of apolipoprotein(a), there would be a reasonable expectation of success to perform the instant method in combination with the modifications, which were known in the art at the time the invention was made, as demonstrated by Baracchini et al. It would have been obvious to substitute the full length antisense taught by Frank et al. with an oligonucleotide 8-30 nucleobases in length as taught by Baracchini et al. to increase stability *in vivo* and *in vitro* by modifying the oligonucleotide as instantly claimed. These modifications could not be performed with the full-length antisense RNA. It would have been obvious to a person of ordinary skill in the art at the time the invention was made, to modify the antisense oligonucleotide with the phosphorothioate, 2'O-methoxyethyl, 5-methylcytosine, or chimeric modifications taught by Baracchini et al., with the motivation to gain the known benefits of these modifications, which include enhanced cellular uptake, enhanced affinity for the nucleic acid target, and increased stability in the presence of nucleases (columns 6 and 8), each being beneficial to the use of targeting a gene. One of ordinary skill in the art at the time the invention was made would have reasonably expected for these modifications to apply to the instant antisense oligonucleotide being delivered and that the modifications would enhance the effectiveness of the antisense oligonucleotide, since the chemistry was well known, as demonstrated by Baracchini et al., Morishita et al. and Frank et al. Therefore, the inventions of claims 2-18, 22 and 25, would have been obvious, as a whole, at the time the instant invention was made.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-19, 22, 25, 30 and 32-35, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-11 and 15-20 of copending application 10/485,113. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain overlapping methods. The instant application and application '113 have the same inventors.

Application '113 teaches a method of inhibiting the expression of human apolipoprotein(a) in cells or tissues comprising contacting said cells or tissues comprising contacting said cells or tissues with a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a), wherein said compound specifically hybridizes with a nucleic acid molecule encoding human apolipoprotein(a) and inhibits the expression of human apolipoprotein(a). Although a specific sequence is not specified, the method of application '113 encompasses SEQ ID NO:23, as instantly claimed (see claims 1, 11 and 15). Claim 11 is specifies that the compound specifically hybridizes with an active site. These claims encompass the same methods present in instant claims 2, 3, 10-13, 19, 22 and 25. Instant claims 33-35 are drawn to a method of inhibiting the expression of apolipoprotein(a) comprising contacting a biological system with an antisense compound 15-30 nucleobases in length that has at least 3 mismatches to human plasminogen. Claims 15 and 16 of application '113 is drawn to a method of inhibiting expression of apolipoprotein(a) or treating a human comprising contacting cells or tissues with a compound or administering said compound, wherein the compound specifically hybridizes with a nucleic acid molecule encoding human apolipoprotein(a). As defined in the specification, page 3, column 1, 100% complementarity is not required for specific hybridization. Instant claim 33 specifies at least 3 mismatches to human plasminogen, which would be encompassed in the breadth of claim 1 of application '113. Additionally, the invention of application '113 encompasses the limitation of instant claim 35, which specifies that the biological system be a transgenic animal since humans exist that would be considered to be transgenic, thus meeting the limitation of 'transgenic animal'.

Application '113 teaches the compound to be an antisense oligonucleotide, wherein the compound can comprise a modified internucleoside linkage, more specifically a phosphorothioate linkage; a modified sugar moiety, more specifically a 2'-O-methoxyethyl sugar moiety; a modified nucleobase, more specifically a 5-methylcytosine modified nucleobase; or the oligonucleotide is a chimeric oligonucleotide (see claims 2 and 4-10). These claims encompass the same methods present in instant claims 4, 5, 8 and 14-17.

Application '113 further teaches a method of treating a human having a disease or condition associated with human apolipoprotein(a) comprising administering a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of apolipoprotein(a) is inhibited, wherein the condition involves abnormal lipid metabolism, abnormal cholesterol metabolism, wherein the condition is atherosclerosis or the disease is cardiovascular disease (see claims 16-20). Therefore, the methods being instantly claimed are obvious over the methods taught by application '113. These claims encompass the same methods present in instant claims 30 and 32.

Claims 2-19, 22, 25 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 15 of copending application 09/923,515. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain overlapping methods. The instant application and application '515 have the same inventors.

Application '515 teaches a method of inhibiting the expression of human apolipoprotein(a) in cells or tissues comprising contacting said cells or tissues comprising contacting said cells or tissues with a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a), wherein said compound specifically hybridizes with a nucleic acid molecule encoding human apolipoprotein(a) and inhibits the expression of human apolipoprotein(a) (claims 1 and 15).

Application '515 teaches the compound to be an antisense oligonucleotide, wherein the compound can comprise a modified internucleoside linkage, more specifically a phosphorothioate linkage; a modified sugar moiety, more specifically a 2'-O-methoxyethyl sugar moiety; a modified nucleobase, more specifically a 5-methylcytosine modified nucleobase; or the oligonucleotide is a chimeric oligonucleotide (see claims 2 and 4-10). Instant claim 33 is drawn to a method of inhibiting apolipoprotein(a) expression comprising contacting a biological system with an antisense compound. As defined in the instant specification, page 27, a biological system is defined as any organism, cell, cell culture or tissue that expresses products of the LPA gene. Therefore, claim 15 of application '515, which is drawn to a method of inhibiting apolipoprotein(a) expression *in vitro*, meets the limitations of instant claim 33. Therefore, the methods being instantly claimed are obvious over the methods taught by application '113.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

Karen Lacourciere
KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER